

The relationship of HLA-B27 and HLA-B51 on Non-Behcet uveitis

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ABSTRACT

Aims: The aim of this study was to investigate the relationship of human leukocyte antigen (HLA)-B27 and HLA-B51 on the clinical characteristics, demographic features, localization, laterality, treatment modalities and visual prognosis in non-Behcet uveitis patients

Study design: Retrospective study.

Place and Duration of Study: Tepecik Eye Training and Research Hospital. January 1999 and March 2009

Methodology: A total of 143 non-Behcet uveitis patients were included. Socio-demographic data and clinical features of the patients were reviewed. The patients were divided into four groups according to HLA-B27 and B-51 positivity which were as follows; HLA B-27 (-) B-51 (-), HLA B-27 (+) B-51 (-), HLA B-27 (-) B-51 (+), and HLA B-27 (+) B-51 (+) groups

Results: Bilateral uveitis and posterior uveitis were more frequent in males in HLA-B27 (+) B51 (+) group, the baseline BCVA values were significantly lower in HLA-B27 (+) B51 (+) group, and also systemic steroid and immunosuppressive treatment were more frequently required to control uveitis attacks in this group. Anterior uveitis was more frequent in the HLA-B27 (-) B51 (-), and HLA-B27 (+) B51 (-) group.

Conclusion: The positivity of both HLA-B27 and HLA-B51 was related with worse visual outcomes in non-Behcet uveitis patients associated with requirement of more aggressive treatment. The negativity of both HLA-B27 and HLA-B51 seemed to be related with better visual outcomes and less number of attacks in non-Behcet uveitis patients.

Key words: Behcet disease, human leukocyte antigen, uveitis.

1. INTRODUCTION

Uveitis is composed of a diverse group of disease entities and is a cause of significant visual impairment accounting for 10% of blindness in the western world [1]. It refers to intraocular inflammation including the uveal tract, and the adjacent structures including vitreous, retina and, optic nerve [1].

The patients with uveitis should be evaluated in many aspects; including anatomic localization of the inflammation, human leukocyte antigen (HLA) typing, etiologic factors and associated systemic diseases which may primarily affect the clinical course and treatment requirements of the patients [2].

Uveitis is widely classified into anterior, intermediate, posterior and panuveitis based on the anatomical involvement [2]. Also Human Leukocyte Antigens (HLA) are closely associated with disease susceptibility in uveitis patients [3]. HLAs are cell surface proteins involved in immune function. HLA molecules present antigenic peptides to generate immune defense reactions. There are two classes of HLA antigens, class I composed of HLA A, B, C and Class II: HLA-DRB, DQB1 and HLA complex defined by the genes of Major Histocompatibility Complex (MHC) [4].

Uveitis is closely associated with class I HLA [3]. HLA-B*51 and B*27 genes frequently play role in the pathogenesis of uveitis. HLA-B*51 is the major gene associated with the pathogenesis of Behcet uveitis [3]. HLA-B*27 is usually related to acute anterior uveitis [5]. On the other hand visual prognosis and clinical course is very different between HLA-B*27 associated uveitis and HLA-B*51 Behcet uveitis [6].

Behcet disease (BD) is a multisystem vasculitic disorder associated with devastating ocular effects, [1] and is dominantly seen on the old silk route between east and west (Korean, Taiwanese, Kuwaiti, Israeli, Turkish, Greek and Tunisian) and associated with HLA-B*51. The effects of HLA on BD is well known; however, there is not any data about its effects on non-Behcet uveitis patients [7] Therefore we classified all of the non-infectious uveitis patients who are not diagnosed as Behcet uveitis as non-Behcet uveitis and aimed to investigate the effect of HLA-B*27 and HLA-B*51 on demographic features, localization, laterality, clinical characteristics, treatment modalities and visual prognosis in this group of uveitis patients.

2. MATERIAL AND METHODS

In this retrospective, comparative study, we reviewed the records of 767 uveitis patients. A hundred and forty-three patients fulfilled the requirements and included in the study. Inclusion criteria were as follows: a minimum follow-up time of 12 months, and a complete laboratory work including HLA typing, and to be in the inactive phase of the disease at the last follow-up visit. Patients were not included in the study, if they were diagnosed as complete or incomplete Behcet disease at any time of the follow-up period. **Patients that are contraindicated to start corticosteroids (diabetes, osteoporosis, hypertension, peptic ulcer etc.) are excluded from the study and consulted on the relevant clinics.** Diagnosis of Behcet disease was made on the basis of the revised criteria of the Behcet Disease Research Committee of Japan in 2003 [3]. Also the patients who were diagnosed as infectious or traumatic uveitis were excluded from the study since the treatment strategy of them were different from the non-infectious cases and their clinical course did not depend on HLA typing. The study was conducted in accordance with the Declaration of Helsinki and an informed consent was obtained from the patients.

At the initial visit, a comprehensive medical and ophthalmologic history was obtained from each patient. Data collected from the patients' records included age, gender, laterality, follow-up time, associated systemic diseases, best corrected visual acuity (BCVA) at the first uveitis attack, BCVA at the last visit, ophthalmologic examination findings, laboratory tests, treatment regimens. Best corrected visual acuity was measured via Snellen scale and converted to LogMAR scale. At all of the visits, slit lamp biomicroscopy, applanation tonometry, fundus examination with 78 diopter non-contact lens was performed. Laboratory tests and radiologic imagings including complete blood count, Toxoplasmosis, Rubella, CMV, Herpes (TORCH) panel, venereal disease research laboratory, angiotensin-converting enzyme test, chest and pelvis x-ray, liver function tests, C-reactive protein, erythrocyte sedimentation rate, HLA-B*51 and HLA-B*27 typing were obtained from each patient..

All patients were questioned for systemic diseases and referred to dermatology and neurology clinics. The patients who were not consulted for rheumatologic evaluation prior to the time of admission were referred to a rheumatologist and medical records were reviewed for patients with a previous rheumatologic follow-up. Ankylosing spondylitis and rheumatoid arthritis diagnosis was made by according to previous reports. A questionnaire form was filled at the initial visit by the physician to assess socio-demographic data including gender, age at presentation and any systemic disease according to the patients history and also addressed the clinical features of the uveitis including anatomical location of the uveitis, bilaterality, clinical course, associated ocular findings (hypopyon, papilla edema, papillitis, vasculitis and maculopathy) according to criteria of the standardization of the uveitis nomenclature (SUN) working group.[2] The classification of the uveitis regarding the localization was made according to the whole follow-up period. Previous ophthalmological evaluation and the use of topical and systemic medications (topical steroids, systemic steroids and immunosuppressive agents) for the treatment of uveitis at presentation were recorded. Since BCVA is affected during active inflammation phases of uveitis, baseline BCVA is defined during the initial uveitis attack and last BCVA is defined after the active inflammation episodes, during remission, at the last follow-up visit.

The given treatment regimens depended on the localization, and the severity of the uveitis. For mild AU, topical steroids (prednisolone acetate) were prescribed for the first uveitis attack. If the inflammation was not able to be controlled with topical steroids periocular corticosteroids (dexamethasone) were applied. When the control of the inflammation could not be achieved with topical and periocular steroid treatment, systemic steroid (prednisolone) and/or systemic immunosuppressive agents (cyclosporine, azathiopurine and methotrexate) were also prescribed. If significant cataract or medically intractable glaucoma developed during the follow-up period, appropriate surgical interventions were performed.

The patients were divided into four groups. The first group included HLA-B27 (-) B51 (-) patients, the second group included HLA-B27 (+) B51 (-) patients, the third group included HLA-B27 (-) B51 (+) patients, and the fourth group included HLA-B27 (+) B51 (+) patients. Primary outcome measures of the study were the laterality, localization and visual prognosis of uveitis and the requirement for systemic steroid and/or immunosuppressant treatment among the four groups. Secondary outcomes were to the gender rates, and complications among the four groups and the systemic associations, etiologic factors of uveitis in the whole study group.

2.1 Data Analysis

Conformity of study variables to normal distribution was controlled with Kolmogorov-Smirnov test and as this was not case, non-parametric tests were applied. One-Way ANOVA (with Bonferroni corrected) test was performed for comparison of age means. Evaluations of visual variables of patients were done by Kruskal Wallis test for independent groups, and Wilcoxon Signed Ranks Test for paired groups. Chi-square test was used to evaluate categorical data (gender, uveitis localization of groups etc.) All statistical analysis were performed with statistical package for social sciences (SPSS Inc., Chicago, IL, USA) version 15. Two-tailed p value less than 0.05 was accepted to be statistically significant.

3. RESULTS AND DISCUSSION

A total of 143 non-Behcet uveitis patients were included in this study. Mean follow up time was 7.6 ± 2.4 years (ranging between 5 and 10 years). Fifty-eighty patients (40.5%) were HLA-B27 (-) B51 (-), 28 patients (19.5%) were HLA-B27 (+) B51 (-), 37 patients (25.8%) were HLA-B27 (-) B51 (+), and 20 patients (13.9%) were HLA-B27 (+) B51 (+). Mean age of patients at presentation between the groups were similar ($p=0.3$) (Table 1) and there was no statistically significant difference in terms of male/female ratio between HLA groups ($p=0.1$) (Table 1).

Table 1. Gender and mean age of HLA groups

	HLA-B27 (-) B51 (-)	HLA-B27 (+) B51 (-)	HLA-B27 (-) B51 (+)	HLA-B27 (+) B51 (+)	Total	P
Male	30 (51.8%)	18 (64.3%)	24 (63.8%)	16 (80.0%)	88 (61.5%)	P ¹ = .1
Female	28 (48.2%)	10 (35.7%)	13 (36.2%)	4 (20.0%)	55 (38.5%)	
Total	58 (100.0%)	28 (100.0%)	37 (100.0%)	20 (100.0%)	143 (100.0%)	
Mean age at presentation	37.3 ± 12.5	37.5 ± 14.7	32.8 ± 13.7	33.4 ± 12.3	35.6 ± 13.3	P ² = .3

HLA, human leukocyte antigen; M, male; F, female.

(P1=Chi-square test, P2=One-Way ANOVA (with Bonferroni corrected))

Ocular damage caused by uveitis depends on several factors like anatomic location, severity, and etiology of the inflammation. Also HLA subgroups are closely associated with disease susceptibility in uveitis patients [8,9].

Anatomic localization of HLA groups were significantly different from each other (p=0.005). Anterior uveitis was more frequent in HLA-B27 (-) B51 (-) (48.6%) and HLA-B27 (+) B51 (-) groups (25.7%). Posterior uveitis was more frequent in HLA-B27 (+) B51 (+) group (40%) (Table 2). There were not any intermediate uveitis cases in the study.

Table 2. Anatomic localization and HLA B27 and B51 relationship of the uveitis patients

	Anterior	Posterior	Panuveitis	Total	P ¹
HLA B27 (-) B51 (-)	34	3	21	58	.005
% within localization	48.6%	30.0%	33.3%	40.5%	
HLA B27 (+) B51 (-)	18	0	10	28	
% within localization	25.7%	.0%	15.9%	19.6%	
HLA B27 (-) B51(+)	15	3	19	37	
% within localization	21.4%	30.0%	30.2%	25.9%	
HLA B27 (+) B51 (+)	3	4	13	20	
% within localization	4.3%	40.0%	20.6%	14.0%	
Total	70	10	63	143	
% within localization	100.0%	100.0%	100.0%	100.0%	

HLA, human leukocyte antigen P1=Chi-square test

Uveitis laterality was also different among the HLA groups (p=0.02). %64.3 of HLA-B27 (+) B51 (-) group was unilateral and %80.0 of HLA-B27 (+) B51 (+) group was bilateral (Table 3).

134 **Table 3. Laterality and HLA B51-B27 relationship of the uveitis patients.**

	Unilaterality	Bilaterality	Total number of patients	<i>P</i> ¹
HLA B27 (-) B51 (-) % within groups	30 51.7%	28 48.3%	58 40.5%	.02
HLA B27 (+) B51 (-) % within groups	18 64.3%	10 35.7%	28 19.6%	
HLA B27 (-) B51(+) % within groups	19 51.4%	18 48.6%	37 25.9%	
HLA B27 (+) B51 (+) % within groups	4 20.0%	16 80.0%	20 14.0%	
Total number of patients % within groups	71 49.7%	72 50.3%	143 100.0%	

135 **HLA, human leukocyte antigen**

136 **P1=Chi-square test**

137 During the study period, the mean attack numbers of HLA-B27 (-) B51 (-), HLA-B27 (+) B51 (-), HLA-
138 B27 (-) B51 (+) and HLA-B27 (+) B51 (+) groups were 1.7±1.0, 2.3±1.3, 2.3±1.5 and 2.5±2.0, respectively (p >
139 0.05). Medical management of uveitis patients were summarized in table 4.

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145 **Table 4. Medical management of uveitis patients**

	HLA B27 (-) B51 N=59	HLA B27 (+) (-)B51 N=28	HLA B27 (-) (-)B51 N=36	HLA B27 (+) (+)B51 N=20	Total (+)number patients	<i>P</i> ¹ of
TOPICAL % within groups	38 64.4%	20 71.4%	15 41.6%	0 .0%	73 51.0%	< .001
TOPICAL + PERIOULAR % within groups	9 15.2%	5 17.8%	5 13.8%	1 5.0%	20 14.0%	
TOPICAL + SYSTEMIC STEROID %within groups	10 16.9%	2 7.1%	10 27.7%	11 55.0%	33 23.0%	
SYSTEMIC STEROID + TOPICAL + PEROCULAR %within groups	0 .0%	0 .0%	0 .0%	2 10.0%	2 1.4%	

SYSTEMIC STEROID+					
TOPICAL +					
IMMUNESUPPRESSIVE	1	1	5	4	11
%within groups	1.6%	3.5%	13.8%	20.0%	7.7%
SYSTEMIC STEROID+					
TOPICAL +					
IMMUNESUPPRESSIVE	0	0	2	2	4
%within groups	.0%	.0%	5.5%	10.0%	2.8%
PEROCULAR					
Total number of	58	28	37	20	143
patients					100.0%
% within groups					

HLA, human leukocyte antigen

P1=Chi-square test

All patients were treated according to anatomical location of the uveitis, degree of intraocular inflammation and etiology of uveitis. HLA-B27 (-) B 51 (-) and HLA-B27 (+) B51 (-) group usually required only topical steroids (1% prednisolone acetate). On the other hand, in addition to topical and periorcular steroid treatment, systemic corticosteroid (prednisolone) and immunosuppressive (cyclosporine, azathiopurine and methotrexate) treatment were required more frequently in HLA-B27 (-) B51 (+), and HLA-B27 (+) B51 (+) group. HLA types and medical management had a statistically significant relationship ($p < .001$) (Table 4).

The visual results of the study were summarized in Table 5.

Table 5. The best corrected visual acuity at baseline and last follow-up visit of the HLA groups.

	Baseline BCVA for right eye	BCVA at the last follow-up for right eye	P^1	Baseline BCVA for left eye	BCVA at the last follow-up for left eye	P^1
HLA B27(-)B51(-)						
Median	0.80	1.00	.03	0.85	1.00	.008
HLA B27(+)B51(-)						
Median	0.90	1.00	.002	0.90	1.00	.001
HLA B27(-)B51(+)						
Median	0.60	1.00	< .001	0.70	1.00	.004
HLA B27(+)B51(+)						
Median	0.30	0.50	.052	0.55	0.75	0.2
P^2	.001	0.6		.007	0.1	

BCVA: Best Corrected Visual Acuity, HLA: Human Leukocyte Antigen.

158 **P1=Wilcoxon Signed Ranks Test. Balded values shows the significance of the change in BCVA from**
159 **baseline to the last follow-up within each HLA group for the right and left eye.**
160 **P2=Kruskal Wallis Test. Balded values shows the significance among the four HLA groups for baseline**
161 **and last follow-up.**

162 The relationship of localization and gender in overall uveitis patients was summarized in table 6.

163 **Table 6. The relationship of localization and gender in overall uveitis patients.**

	Male	Female	Total number of patients	Male/Female	<i>P</i> ¹
Anterior uveitis	36 (51.4%)	34 (48.5%)	70 (49.0%)	1.05	.005
Posterior uveitis	4 (40.0%)	6 (60.0%)	10 (7.0%)	0.66	
Panuveitis	47 (74.6%)	16 (25.3%)	63 (44.0%)	2.93	
Total number of patients	88 (61.5%)	55 (38.5%)	143 (100.0%)	1.6	

164 **P1=Chi-square test**

166 The relationship between localization and laterality of uveitis were summarized in table 7.

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169 **Table 7. Localization of uveitis and laterality relationship.**

	Unilaterality	Bilaterality	Total number of patients	<i>P</i> ¹
Anterior uveitis	43 (61.4%)	27 (38.6%)	70 (49.0%)	.01
Posterior uveitis	2 (20.0%)	8 (80.0%)	10 (7.0%)	
Panuveitis	26 (41.3%)	37 (58.7%)	63 (44.0%)	
Total number of patients	71 (49.7%)	72 (50.3%)	143 (100.0%)	

P1=Chi-square test

There was not a statistically significant relationship between localization of uveitis patients and laterality.

Uveitis is commonly diagnosed in the third decade of life [10]. In our study mean age of non-Behcet uveitis patients at presentation was 35.1 ± 24.8 years which was compatible with the previous reports [10,11].

There was no difference in terms of male/female ratio among the HLA groups in this study, and this was consistent with a previous study from Turkey by Tugal-Tutkun et al [6].

Anterior uveitis accounts for 50% to 92% of uveitis cases in the Western countries and 28% to 50% of uveitis cases in Asian countries, such as, Korea, Japan, and India.[10,11] In Turkey the frequency AU was reported between 28.5% and 90% [7]. In our study AU accounted for 49.0% of total uveitis cases, and this was similar to previous studies [10,12].

There was a statistically significant difference among the HLA groups in regards of anatomic localization and laterality in this study. Unilaterality was statistically frequent in HLA-B27 (+) B51 (-) group (64.3%) and bilaterality was statistically frequent in HLA-B27 (+) B51 (+) group (80.0%). These findings were consistent with previous studies regarding that HLA-B27 (+) B51(-) associated uveitis typically caused a recurrent, dominantly unilateral disease [13,14]. Rosenbaum et al. showed that HLA- B27 was positive in 80% of the patients with unilateral, acute and recurrent uveitis [15]. On the other hand bilaterality was reported to be more frequent in HLA-B27 (+) B51 (+) group of Behcet patients [11]. These data may show that HLA-B27 positivity alone tends to be associated with unilateral uveitis, but when both HLA-27 and HLA-B51 were positive, bilaterality was more frequent. The HLA-B51 (+) cases were associated with posterior segment involvement more frequently than the HLA-B51 (-) cases. In the literature there are some studies supporting this phenomenon [16].

There was also a remarkable difference between the groups in terms of anatomic localization and HLA types. Anterior uveitis was significantly more frequent in HLA-B27 (-) B51 (-), and HLA-B27 (+) B51 (-) group. Posterior uveitis was significantly more frequent in HLA-B27 (+) B51 (+) group.

There was a statistically significant difference among the HLA groups in regards of medical management in the study. While most of the HLA B51 (-) patients could have been treated with only topical steroids, the HLA B51 (+) patients and especially HLA B27 (+) B51 (+) subgroup required systemic steroids and/or immunosuppressives.

In the literature there are few data about the effect of HLA-B51 positivity on visual outcomes in non-Behcet uveitis patients. The change in BCVA was found to be statically better in the HLA groups, except in HLA-B27 (+) B51 (+) group. This may be due to heterogeneity and low number of patients.

Male sex and younger age of onset was reported to be negative prognostic factors for Behcet disease and the frequency of HLA-B51 antigen was reported to be higher in male patients with uveitis in Japan [19,20]. These findings were contrast to our findings of non-Behcet uveitis patients.

In our study bilateral (%80) and posterior uveitis (%40) was found to be frequent in HLA-B27 (+) B51 (+) group. The change in BCVA was significantly lower in this group, and also systemic steroid and immunosuppressives were more frequently required for the treatment. On the other side, AU was more frequent in patients with HLA-B27 (-) B51 (-), and HLA-B27 (+) B51 (-) group.

In the literature, the relationship between the Behcet Disease and HLA subgroups was evaluated in several studies [1]. However, this study is the first to evaluate the relationship of HLA-B27 and HLA-B51 on non-Behcet uveitis patients in terms of anatomic localization, visual acuity, treatment regimens. Limitations of this study include the retrospective design and the irregularity of follow-up period among the patients. Also we did not perform advanced laboratory tests to exclude the infectious uveitis like aqueous tapping and molecular

biology testing for viral uveitis, only serum TORCH panel was performed. Therefore we might have missed some of the infectious anterior uveitis cases. Since there are a few studies about non-Behçet uveitis we could not compare our all results with the literature.

Strengths of the study include the relatively good number of non-Behcet uveitis patients and the center of the study. The study was conducted in a tertiary center which was referred from many state hospitals in Aegean Region of Turkey; therefore the study may reflect the patient characteristics of the non-Behcet uveitis patients in Aegean Region of Turkey

4. CONCLUSION

The relationship between HLA subtypes and Behcet disease was evaluated in previous studies. To our knowledge, this study is the first to investigate the relationship of HLA-B27 and HLA-B51 on Non-Behcet uveitis patients. Bilaterality and posterior uveitis was found to be more frequent in the group of HLA-B27 (+) B51 (+) patients. Also systemic steroid and immunosuppressive requirement was more frequent. Also in contrast to the other three groups, the change in BCVA from baseline to the last follow-up visit was not statistically better in this group. On the other side, anterior uveitis was more frequent in HLA-B27 (+) B51 (-) group.

As a result positivity of both HLA-B27 and B-51 seems to be a negative prognostic factor for non-Behcet uveitis patients. Further studies are required to delineate the prognostic factors for this group of patients

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